TRANSLATION

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Form PCT/IPEA/416
GP04-1022PCT		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/JP2004/017586	26.11.2004	26.11.2003

International Patent Classification (IPC) or national classification and IPC

A61K45/00, A61P1/00, 1/04, 29/00, 31/04, 43/00, C12N15/09, C12Q1/68, G01N33/15, 33/50

Applicant

DAIICHI PHARMACEUTICAL CO., LTD.

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

3. This report is also accompanied by ANNEXES, comprising:

   a. ☒ *(sent to the applicant and to the International Bureau)* a total of 2 sheets, as follows:

      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).

      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.

   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s))

      _____, containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☒	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
Name and mailing address of the IPEA/JP Facsimile No.	Authorized officer Telephone No.

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/JP2004/017586

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ This report is based on translations from the original language into the following _____, which is the language of a translation furnished for the purposes of:

☐ international search (Rule 12.3 and 23.1(b))

☐ publication of the international application (Rule 12.4)

☐ international preliminary examination (Rule 55.2 and/or 55.3)

2. With regard to the **elements** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

☐ the international application as originally filed/furnished

☒ the description:

pages 1-24 as originally filed/furnished

pages* _____ received by this Authority on _____

pages* _____ received by this Authority on _____

☒ the claims:

nos. 1-14 as originally filed/furnished

nos.* _____ as amended (together with any statement) under Article 19

nos.* 15 received by this Authority on 29.06.2005

nos.* _____ received by this Authority on _____

☒ the drawings:

sheets Fig. 1-4 as originally filed/furnished

sheets* _____ received by this Authority on _____

sheets* _____ received by this Authority on _____

☐ a sequence listing and/or any related table(s) – see Supplemental Box Relating to Sequence Listing.

3. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages _____

☐ the claims, nos. _____

☐ the drawings, sheets/figs _____

☐ the sequence listing *(specify)*: _____

☐ any table(s) related to sequence listing *(specify)*: _____

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

☐ the description, pages _____

☐ the claims, nos. _____

☐ the drawings, sheets/figs _____

☐ the sequence listing *(specify)*: _____

☐ any table(s) related to sequence listing *(specify)*: _____

* *If item 4 applies, some or all of those sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/JP2004/017586

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application

☒ claims Nos. 1-4,15

because:

☒ the said international application, or the said claims Nos. 1-4
relate to the following subject matter which does not require an international preliminary examination (*specify*):

The subject matter of claims 1-4 relates to methods for treatment of the human body by therapy.

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. _____
are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for said claims Nos. 1-4,15

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form
☐ has not been furnished
☐ does not comply with the standard

the computer readable form
☐ has not been furnished
☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See Supplemental Box for further details.

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/JP2004/017586

Box No. V **Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	5-14	YES
	Claims		NO
Inventive step (IS)	Claims	5-14	YES
	Claims		NO
Industrial applicability (IA)	Claims	5-14	YES
	Claims		NO

2. Citations and explanations (Rule 70.7)

Document 1: Yoo, Nam Jin et al., "Nod1, a CARD protein, enhances pro-interleukin-1β processing through the interaction with pro-caspase-1", Biochem. Biophys. Res. Commun., 2002, Vol. 299, pages 652 to 658

Document 2: Ogura, Yasunori et al., "Nod2, a Nod1/Apaf-1 family member that is restricted to monocytes and activates NF-κB", Journal of Biological Chemistry, 2001, Vol. 276, pages 4812 to 4818

Document 3: Lee, Sug Hyng et al., "COP, a caspase recruitment domain-containing protein and inhibitor of caspase-1 activation processing", Journal of Biological Chemistry, 2001, Vol. 276, pages 34495 to 34500

Novelty and inventive step

Claims 5 to 14

Document 1 indicates that by bonding with pro-caspase-1, NOD1 promotes an increase in quantity of procaspase, and promotes the processing and secretion of pro-IL-β. which is an inflammatory cytokine (page 652,

Abstract).

Document 2 indicates that document 2 has a structural similarity to document 1 in terms of the amino acid sequence and in having CARD, and that it has the same function in activating NF-κB, for example (page 4812, Abstract).

Document 3 indicates that a protein which suppresses the secretion of caspase-1 reliant IL-1β by inhibiting an increase in quantity of procaspase, can be used in the treatment of inflammation (page 34495, Abstract).

Meanwhile, in the response to the written opinion dated 29 June 2005, the applicant asserts that because:

(1) Document 2 indicates that NOD2 does not bond with caspase
(2) Reference document 1 submitted by the applicant on the same date indicates that NOD1 bonds with caspase-4, 9 in addition to caspase-1, but document 2 indicates that NOD2 does not bond with any of these
(3) Ipaf which has the same CARD domain as NOD2 bonds with procaspase-1, but cannot activate procaspase-1
(4) ICEBERG and COP which also have CARD inhibit the activation of caspase-1 and the production of IL-1β,

from the disclosure stating the homogeny of NOD2 and NOD1 in terms of the amino acid sequence, and that both NOD2 and NOD1 had CARD, it was unclear whether or not NO2 was able to achieve activation by bonding with procaspase-1.

Taking into account the above assertion and the disclosure of documents 1 to 5 submitted by the applicant, documents 1 to 3 neither indicate nor suggest

Box No. V **Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

that even with homogeny in terms of the amino acid sequence and the existence of CARD, NOD2 bonds with the same procaspase 1 as NOD1.

Therefore the invention set forth in claims 5 to 14 is novel and involves an inventive step.

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

Claims 6, 8 and 12

Claim 6 of this application contains the wording "an agent to inhibit an increase in quantity in procaspase-1, characterized in inhibiting bonding between NOD2 and procaspase-1(omitted)", but said claim merely indicates that said agent is "characterized in inhibiting", and said claim does not indicate what type of substance is contained in said inhibiting agent as an active ingredient.

That being the case, claim 6 of this application and claims which refer back to claim 6 are unclear.

The same applies to claims 8 and 12 and the claims which refer back to these claims.

Claims 6 to 13

Claims 6 to 13 set forth an agent for inhibiting an increase in the quantity of caspase-1 which is characterized in inhibiting bonding between NOD2 and procaspase, and an agent for the treatment of inflammatory disorders containing said inhibitor.

However, the description of this application only indicates that NOD2 bonds with procaspase-1, NOD2 promotes an increase in quantity in procaspase-1, and NOD2 promotes the secretion of IL-1β dependent on procaspase-1, and there is no specific disclosure that a compound which could actually inhibit bonding between the two was identified, and that inflammatory disorders were treated by administering said compound.

That being the case, the inventions set forth in claims 6 to 13 are not fully supported by the

Box No. VIII **Certain observations on the international application**

description.